STUDY KRT-232-114

ABBREVIATED CLINICAL STUDY REPORT

Study Title	An Open-Label, Multicenter, Phase 2 Study Assessing the Safety and Efficacy of KRT-232 or TL-895 in Janus-associated Kinase Inhibitor Treatment-Naïve Myelofibrosis
Brief Title	Safety and Efficacy of KRT-232 or TL-895 in Janus-associated Kinase Inhibitor Treatment-Naïve Myelofibrosis
Study Number	KRT-232-114
Study Phase	Phase 2
Name of Investigational Drugs	KRT-232 (navtemadlin) or TL-895
Indication	Myelofibrosis
Study Sponsor	Kartos Therapeutics, Inc. 275 Shoreline Drive, Suite 300 Redwood City, CA 94065
Study Initiation Date	26 July 2021 (first subject first visit)
Early Study Termination Date	18 July 2024 (last subject last visit) The data and analyses presented in this report are based on a database lock date of 06 August 2024
Regulatory Agency Identifier Numbers	IND: 151474 EudraCT: 2020-005642-42 ClinicalTrials.gov: NCT04878003
Report Date	14 February 2025
This study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.	

SYNOPSIS

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Number of Study Centers and Countries	This study was conducted at 16 centers in 7 countries (Brazil, Bulgaria, Georgia, Mexico, Poland, Russia and Ukraine).
Study Period	26 July 2021 (first subject first visit) 18 July 2024 (last subject last visit; early study termination date)
Rationale	Myelofibrosis (MF; including primary myelofibrosis [PMF], post-polycythemia vera MF [post-PV MF], or post-essential thrombocythemia MF [post-ET MF]) is a clonal myeloproliferative neoplasm characterized by progressive bone marrow fibrosis, dysplastic megakaryocyte hyperplasia, and extramedullary hematopoiesis, resulting in ineffective erythropoiesis (Cervantes 2009). Patients often harbor molecular mutations (eg, JAK2, MPL, CALR) that drive MF pathogenesis (Pikman 2006; Hussein 2009). Ruxolitinib, a JAK inhibitor, is approved in the United States and European Union for intermediate- and high-risk MF (Jakafi® US Prescribing Information); while it reduces splenomegaly and improves symptoms, it does not halt disease progression, and symptoms often reappear shortly after discontinuation (Verstovsek 2012). High rates of treatment failure or unacceptable adverse effects have also been noted in long-term use (Verstovsek 2017). Fedratinib, a selective JAK2 inhibitor, was approved in the US for adults with intermediate-2 or high-risk MF. While fedratinib effectively reduces splenomegaly and symptom burden in MF patients, it carries significant side effects, including a black box warning for encephalopathy (Inrebic® Prescribing Information). Although ruxolitinib and fedratinib provide symptomatic relief, their mechanisms of action are associated with significant disruptions to normal hematopoiesis, and they have not been proven to prolong survival or reduce the risk of leukemic transformation. There remains a significant unmet clinical need for the treatment of patients with MF. KRT-232 (navtemadlin) targets the mouse double minute 2 homolog (MDM2)/TP53 interaction, restoring TP53 tumor-suppressor function in TP53 wildtype ($TP53^{WT}$) tumor cells (Sun 2014). The great majority of MF cases

harbor TP53^{WT} tumor cells (Grinfeld 2018) and overexpression of MDM2 is reported in CD34+ MF cells (Lu 2017). This suggests a role for targeting the MDM2:p53 interaction as a therapeutic strategy to induce apoptosis in MF tumor cells. In the KRT-232-101 clinical study (NCT03662126), KRT-232 demonstrated compelling monotherapy activity in MF patients who are relapsed or refractory to JAK inhibitor treatment (Al-Ali 2020).

TL-895 is an orally bioavailable, small molecule, targeted kinase inhibitor that selectively inhibits BTK and BMX. [redacted]

A BTK inhibitor with additional activity against BMX has the potential to provide multiple synergies to counteract mechanisms in the pathogenesis of MF. [redacted] In patients with MF, therapeutics that target the abnormal behavior of these cells should result in improvement of constitutional symptoms, clinically meaningful reductions in spleen volume and disease burden and the potential for disease modification and reduction in bone marrow fibrosis. Unlike currently approved JAK inhibitors, the effects of TL-895 on the pathogenic mechanisms that drive MF are expected to occur without significant disruptions to normal hematopoiesis.

Study Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To assess the spleen response rate of each arm at Week 24.	The proportion of subjects achieving ≥ 35% SVR at Week 24 by MRI/CT (central review).
Secondary Objectives	**Secondary Endpoints**
To assess the change in total symptom score (TSS) for each arm	The proportion of subjects achieving ≥ 50% reduction in TSS at Week 24 by Myelofibrosis Symptom Assessment Form (MFSAF) v4.0.
To determine the safety and tolerability of the treatment in each arm.	Laboratory tests, AEs, SAEs, ECGs, vital signs.
To characterize the pharmacokinetic profile of KRT-232 (Arm 1) or TL-895 (Arms 2, 3 and 4)	KRT-232 and acyl glucuronide metabolite (M1) or TL-895 pharmacokinetic (PK) parameters, including but not limited to: • Maximum observed concentration (C_{max}) • Time of maximum observed concentration (T_{max}) • Area under the plasma concentration-time curve (AUC)

Additional planned objectives and endpoints are provided in the Statistical Analysis Plan in Appendix 9.1.9.

Methodology	This Phase 2, open-label, multicenter, 2-stage clinical study evaluated the safety, tolerability, and efficacy of navtemadlin or TL-895 in subjects with primary, post-PV, or post-ET TP53 wild-type MF who were treatment-naïve to any JAK inhibitor. Stage 1 assessed initial safety, tolerability, and efficacy, followed by expansion in Stage 2. Eligible subjects were to be enrolled into [redacted]: • Arm 1: Navtemadlin 240 mg administered orally (po) once daily (QD) Days 1-7 of a 28-day cycle • Arm 2: TL-895 150 mg po twice daily (BID) in 28-day cycles [redacted] The Treatment Period extended from the first dose of study drug (ie, Cycle 1 Day 1) until the End-of-Treatment visit, which occurred 28 days after the last dose of study drug. During the Treatment Period, subjects were to receive treatment until the Week 12 response assessment or disease progression, whichever occurred first. At Week 12, subjects with an SVR35 could continue treatment until disease progression. [redacted] The Follow-up Period began 12 weeks after the last dose of study drug. The Follow-up Period continued every 12 weeks until death, loss to follow-up, withdrawal of consent, end of study, whichever occurred first. Enrollment was to continue until 14 evaluable subjects per arm were enrolled. The Safety Review Committee (SRC) met approximately every 3 months during the conduct of the study to review safety and efficacy data. After all subjects completed the Week-24 assessment, the SRC was to determine expansion into Stage 2. [redacted]
Statistical Analyses	A detailed methodology for summary and statistical analysis of the data collected in this study is documented in the Statistical Analysis Plan (Appendix 9.1.9)
Number of Subjects (Planned and Analyzed)	In Stage 1, [redacted] 32 subjects were enrolled and analyzed. [redacted] As the study was terminated during Stage 1, no subjects were enrolled or analyzed in Stage 2.
Diagnosis and Main Criteria for Inclusion and Exclusion	**Key Inclusion Criteria** Subjects could be enrolled in the study if they had: • Confirmed diagnosis of PMF, post–PV-MF, or post–ET-MF, as assessed by treating physician according to the World Health Organization criteria • Palpable spleen measuring ≥ 5 cm below the left lower costal margin or spleen volume of ≥ 450 cm^3 by MRI or CT scan assessment.

	[redacted] • High-risk, or intermediate-1 and 2 risk, defined by Dynamic International Prognostic System (DIPSS). • Adequate hematological, hepatic, and renal organ function (as per protocol definition and within 28 days prior to the first dose of study drug). **Key Exclusion Criteria** Subjects were ineligible to participate in the study if they: • Arm 1 (navtemadlin) – Were positive for p53 mutations. – Received prior MDM2 inhibitor therapy or p53-directed therapy. • Arms 2[redacted] – Received prior treatment with any BTK, BMX inhibitor. [redacted] – Required anticoagulation with warfarin or equivalent vitamin K antagonists within 7 days of the first dose of study drug. • Received prior treatment with any JAK inhibitor. • Received chemotherapy, immunomodulating therapy, biologic therapy, or radiation therapy within 14 days prior to the first dose of study drug. Hydroxyurea must have been discontinued at least 14 days prior to the first dose of study drug.
Study Drug, Dose, Mode of Administration, and Batch Number(s)	The study drugs were navtemadlin and TL-895. Navtemadlin was administered at a dose of 240 mg po QD on Days 1-7 of a 28-day cycle to subjects in Arm 1. [redacted] TL-895 was to be administered at a dose of 150 mg (Arm 2)[redacted] po BID in 28-day cycles. [redacted]
Duration of Study Intervention	Subjects were to receive treatment until the Week 12 response assessment or disease progression, whichever came first. At Week 12, subjects with at least a 35% SVR could continue treatment until disease progression.[redacted] The study was to be considered complete 2 years after the last subject was enrolled.

Summary of Results

A total of 32 eligible subjects enrolled into the study and were allocated to a treatment arm (Arm 1, n = 14; Arm 2, n = 16 [redacted].

Disposition

All subjects discontinued study drug. In Arms 1 and 2, the most frequent reason for study drug discontinuation was physician decision (Arm 1, 35.7%; Arm 2, 43.8%) [redacted]

All subjects discontinued the study. The most frequent reason for study discontinuation across all arms was early study termination (Arm 1, 78.6%; Arm 2, 81.3% [redacted]). The median time on study was 16.74 months (Arm 1), 13.95 months (Arm 2) [redacted]

Demographic and Other Baseline Characteristics

Arm 1 (Navtemadlin 240 mg QD days 1-7 of a 28-day cycle):

In Arm 1, the median age was 62 years, and most subjects were male (10 subjects, 71.4%) and white (14 subjects, 100%). All subjects were $TP53^{WT}$. Most subjects had an Eastern Cooperative Oncology Group performance status (ECOG) of 1 (11 subjects, 78.6%), a Dynamic International Prognostic System Score (DIPSS) of intermediate-1 (13 subjects, 92.9%) and primary MF (8 subjects, 57.1%), with a median time since diagnosis of 10.2 months (range: 3.4 to 85.6 months). The median spleen size was 1635.1 cm2 (range: 945 to 3861) and the baseline MFSAF score was 19.55 (range: 11.7, 54.3). Most subjects were transfusion independent (12 subjects, 85.7%) with a median hemoglobin level of 117.6 g/L.

Arm 2 (TL-895 150 mg BID):

In Arm 2, the median age was 69 years, and most subjects were male (11 subjects, 68.8%) and white (13 subjects, 81.3%). Most subjects had an ECOG of 1 (15 subjects, 93.8%), half had a DIPSS of intermediate-1 (8 subjects, 50.0%) and most had primary MF (13 subjects, 81.3%), with a median time since diagnosis of 4.7 months (range: 0.8 to 402.8 months). The median spleen size was 2097.7 cm2 (range: 659 to 7111) and the baseline MFSAF score was 19.21 (range: 9 to 36.6). Most subjects were transfusion independent (12 subjects, 75%) with a median hemoglobin level of 102.3 g/L.

[redacted]

Exposure

Subjects received a median of 5.5 cycles of navtemadlin (range: 1, 30) over a median treatment duration of 183 days (range: 7, 823). Subjects in Arm 2 received TL-895 over a median treatment duration of 122.5 days (range: 15, 588) [redacted]

Efficacy Results

As the study was terminated early because of a sponsor decision unrelated to safety, only the primary endpoint and the first secondary efficacy endpoint are presented. Analyses were performed on the Safety Population, and no hypotheses testing was conducted.

The primary endpoint was the proportion of subjects achieving a $\geq 35\%$ reduction in spleen volume (SVR35) from Baseline to Week 24, as assessed by MRI or CT scan (central review). In Arm 1, 9 of 14 subjects remaining on study had both a baseline and Week 24 spleen measurement. At Week 24, 6 of 16 subjects in Arm 2 [redacted] had both a baseline and Week 24 spleen volume measurement.

Clinical activity was observed with navtemadlin (240 mg QD on days 1-7 of a 28-day cycle; Arm 1) where a total of 14.3% of subjects (2/14) achieved SVR35 by MRI/CT scan (central review) at Week 24 [redacted] In subjects treated with TL-895 ([redacted] 150 mg BID [Arm 2] [redacted]), no subject achieved a SVR35 at Week 24.

[redacted]

The first secondary endpoint was the proportion of subjects achieving ≥ 50% reduction in TSS at Week 24 by MFSAF v4.0. Clinical activity was observed with navtemadlin (240 mg QD on days 1-7 of a 28-day cycle; Arm 1) where a total of 28.6% of subjects (4/14) achieved TSS50 by MFSAF v4.0 at Week 24 [redacted] In subjects receiving TL-895 150 mg BID (Arm 2), a total of 12.5% of subjects (2/16) achieved TSS50 by MFSAF v4.0 at Week 24. [redacted]

[redacted]

Pharmacokinetic Results

Pharmacokinetic results are reported separately in the KRT-232-114 Pharmacokinetic Report K2024004-CP (Appendix 9.1.13).

Safety Results

Arm 1 (Navtemadlin 240 mg QD days 1-7 of a 28-day cycle):

In Arm 1, 12 of 14 (85.7%) subjects receiving navtemadlin experienced at least one treatment-emergent adverse event (TEAE; Table 1). The most frequently reported TEAEs (occurring in ≥ 15% of subjects) were diarrhea and anemia (5 subjects each, 35.7%), neutropenia, nausea, and thrombocytopenia (4 subjects each, 28.6%), and COVID-19 (3 subjects, 21.4%).

Serious TEAEs were reported in 5 subjects (35.7%) and included anaemia, neutropenia, abdominal pain, oesophageal haemorrhage and sepsis (1 subject each; Table 14.3.1.2.3). [redacted] no serious TEAEs were considered treatment related. [redacted]. No deaths were reported.

Arm 2 (TL-895 150 mg BID):

In Arm 2, 12 of 16 subjects (75%) receiving TL-895 150 mg BID experienced at least one TEAE (Table 1). The most frequently reported AE (≥ 15% of subjects) by PT in subjects were anaemia (5 subjects; 31.3%) and fatigue (3 subjects; 18.8%).

Serious TEAEs were reported in 5 subjects (31.3%) and included anaemia, thrombocytopenia, fatigue, oedema peripheral, pulmonary sepsis (1 subject each), and gastrointestinal haemorrhage (2 subjects; Table 14.3.1.2.3). [redacted] no serious TEAEs were considered treatment-related.

[redacted]

[redacted]. No deaths were reported.

[redacted]

Conclusions

- As the study was terminated early because of a sponsor decision unrelated to safety, only 32 of the planned 104 subjects were enrolled.
- Although no formal efficacy analyses were performed, clinical activity was observed with navtemadlin (240 mg QD on days 1-7 of a 28-day cycle; Arm 1). A total of 14.3% of subjects (2/14) achieved SVR35 by MRI/CT scan (central review) and 28.6% (4/14) achieved TSS50 by MFSAF v4.0 at Week 24.
- [redacted] no subject receiving TL-895 [redacted] achieved an SVR35 by MRI/CT scan at Week 24. In subjects receiving TL-895 150 mg BID (Arm 2), a total of 12.5% of subjects (2/16) achieved TSS50 by MFSAF v4.0 at Week 24. [redacted]
- Navtemadlin and TL-895 were safe and well tolerated. The most frequently reported treatment-related TEAEs were consistent with the known safety profiles of navtemadlin and TL-895 derived from other clinical studies. No new or additional safety signals were observed in this study.

Date and Version of this Report: 14 February 2025